Phase Ib study using patient-derived tumor cells expressing a streptococcal antigen in patients with asymptomatic indolent non-Hodgkin lymphoma

Protocol #1307-1239

Presentation Overview

- Indolent non-Hodgkin lymphoma (iNHL)
- Rationale for proposed study
- IFx-hu1.0
- Pre-clinical studies
- Ph 1b IFx-hu 1.0 iNHL study protocol

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Lymphoma

- Group of diseases
  - Hodgkin's disease (Hodgkin lymphoma)
  - Non-Hodgkin lymphoma

- Cancers caused by growth of malignant lymphocytes in lymph nodes and other tissues

2013 Estimates (USA)

	New Cases	Deaths
Hodgkin Lymphoma	9,290	1,180
Non-Hodgkin Lymphoma	69,740	19,020

CA Cancer J Clin 63:11, 2013

Lymphoma Behavior

- Some are VERY aggressive
  - Difficult to treat, but often curable
- Some are moderately aggressive
  - Some are hard to treat, but more likely to be cured
  - Others are harder to treat and less likely to be cured
- Some are slow growing, with few symptoms
  - Easy to treat, but HARD to cure

Current Treatment Options for Indolent Lymphoma

Treatment Options:

- Observation (watch and wait)
- Radiation
- Single-agent therapy
- Combination chemotherapy
- Interferon
- Monoclonal antibodies
- Bone marrow transplantation
- Antisense molecules
- Targeted agents
- Vaccines

Treatment Considerations:

- Age
- Co-morbidities
- Symptoms
- Side effects of treatment
- Quality of life
- Costs of treatment
- Goals of treatment
- Availability of trial

10-Year Survival Trends for Low-grade Lymphoma (USA)

Age Range	Survival	
	1990 – 1992	2002 – 2004
15 – 44	64%	84%
45 – 54	59%	81%
55 – 64	54%	73%
65 – 74	49%	70%
≥ 75	31%	49%
Total	52%	72%

Arch Int Med 168:469, 2008

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Rationale for Proposed Study

- People still die from indolent lymphoma
- Current treatments may be associated with significant morbidity and mortality
- There is a need for novel treatment approaches
- IFx-hu1.0 mechanism of action relies on ability to elicit an immune response
- Patients with asymptomatic indolent lymphomas are an ideal population for treatment with this vaccine in this Phase 1 study

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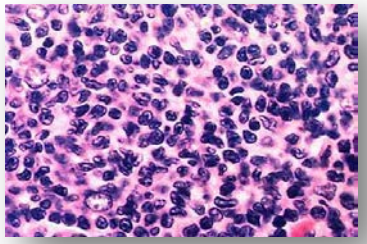
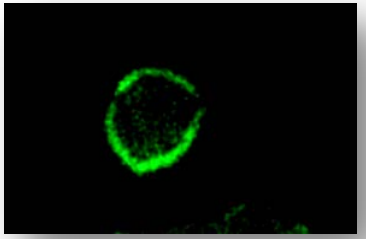
IFx-hu1.0

- Autologous whole-cell cancer vaccine for iNHL
  - Lymphoma cells (from lymph node biopsy)
  - Transfected *ex vivo* to express *Emm55* in cytosol and on cell surface



- *Emm55* is a highly immunogenic/non-superantigenic *S. pyogenes* serotyping Ag
- Cells are cultured (48 hr) following transfection to allow expression of *Emm55*
- Cells are irradiated prior to intradermal administration to prevent replication



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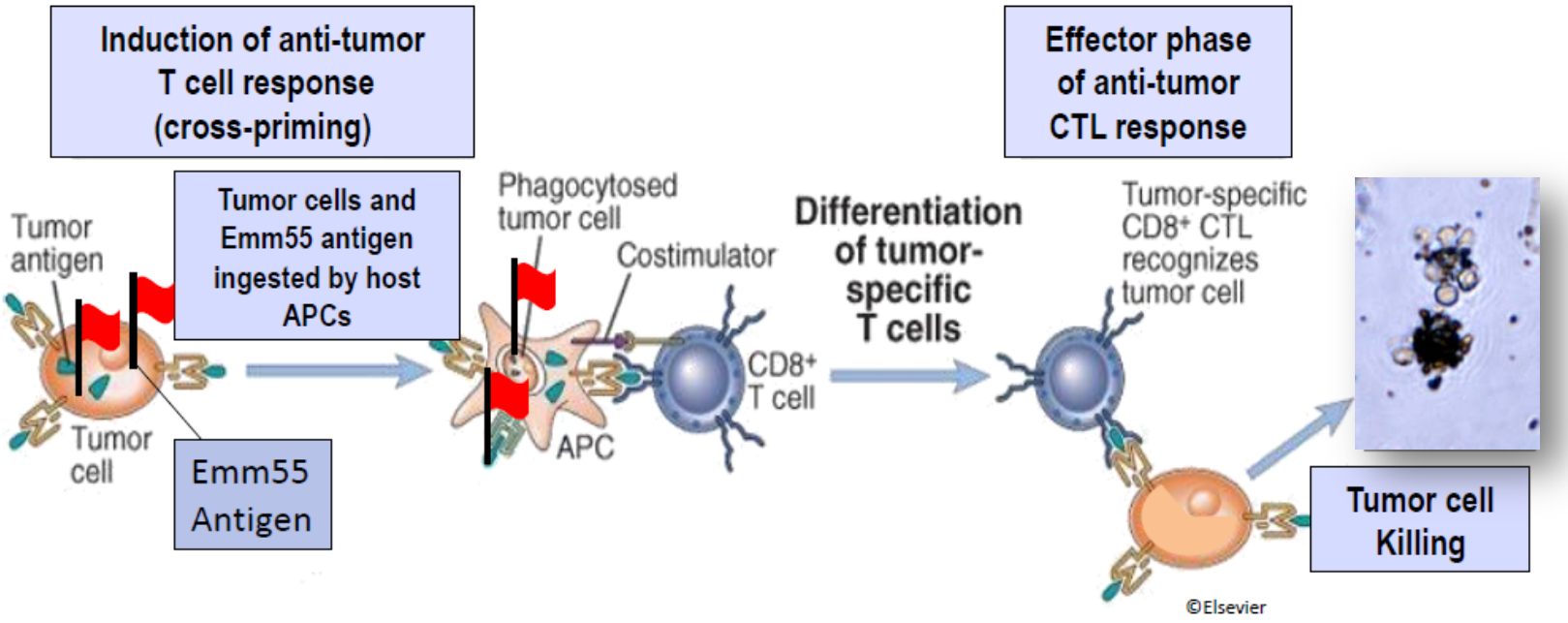
Rationale for IFx-hu1.0

- Provides immune priming signal (universal TSA)
- Elicits tumor-specific immune response



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Pre-clinical Studies

ImmuneFx™ whole cell vaccine technology studied in the following:

- Murine neuroblastoma (N-2a) model (syngeneic)
- Naturally-occurring canine lymphoma (autologous)
- Multiple indications in companion animals (autologous) (19 malignancies, 45 breeds, 4 species)

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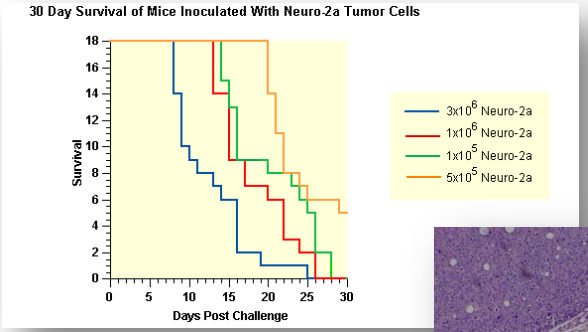
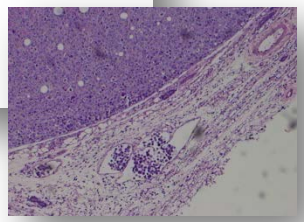
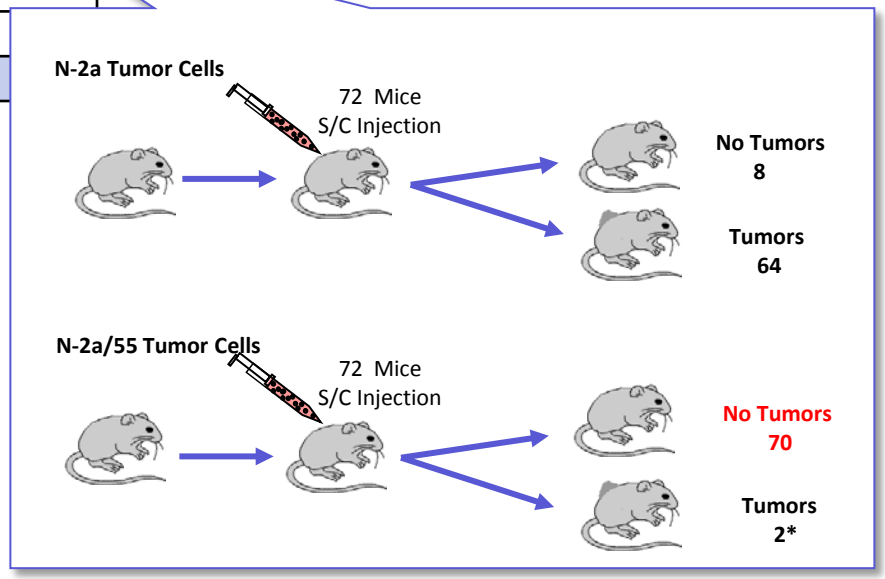
Tumorgenicity of N-2a & N-2a/Emm55 in A/J Mice

Group	Inoculums	# of Mice Inoculated	# of Mice with Tumors	Day of Onset/ # Tumors Observed
1	$3x10^6$/N-2a	18	17	6/5
2	$1x10^6$/N-2a	18	17	11/7
3	$5x10^5$/N-2a	18	17	11/2
4	$1x10^5$/N-2a	18	13	17/1
	TOTAL	**72**	**64 (89%)**	
5	$3x10^6$/N-2a/Emm55	18	2	11/2
6	$1x10^6$/N-2a/Emm55	18	0	0
7	$5x10^5$/N-2a/Emm55	18	0	0
8	$1x10^5$/N-2a/Emm55	18	0	0
	TOTAL	**72**	**2* (2.8%)**	







*Tumors regressed completely

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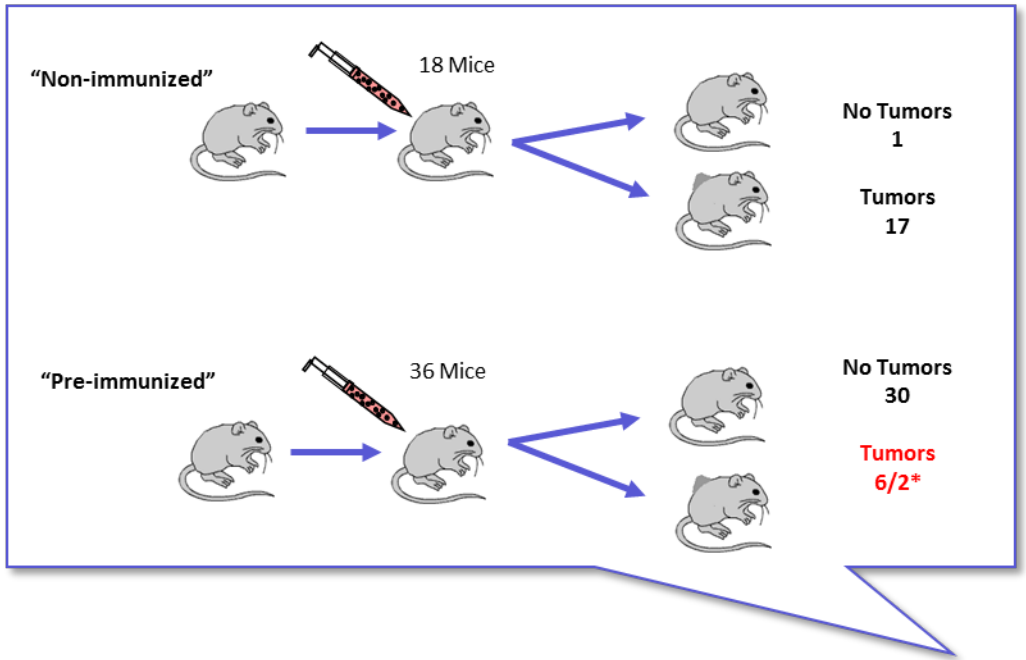
Prophylactic Effect of N-2a/Emm55 in A/J Mice



Group	Vaccine Dose	# of Mice	Challenge Dose	# Mice with Tumors	Day of Onset/ # Tumors Observed**
1	$3x10^6$/N-2a/Emm55	18	$3x10^6$/N-2a	6* (33%)	7/1
2	$1x10^6$/N-2a/Emm55	18	$3x10^6$/N-2a	2 (11%)	33/2
3	None	18	$3x10^6$/N-2a	17 (94%)	6/7

*2 tumors regressed by day 32 post challenge

* * number of mice with tumors on that day

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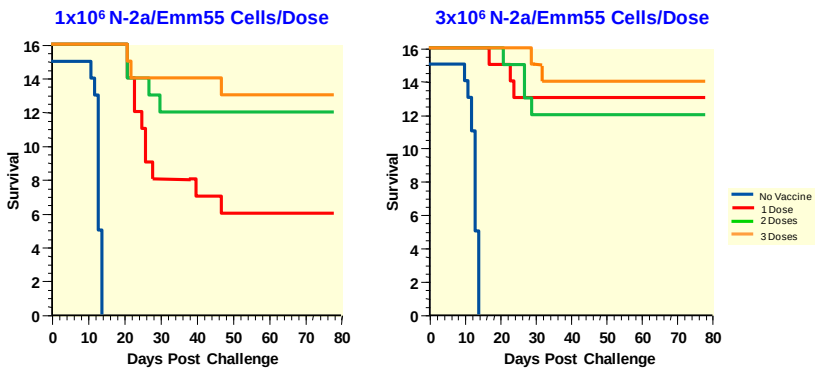
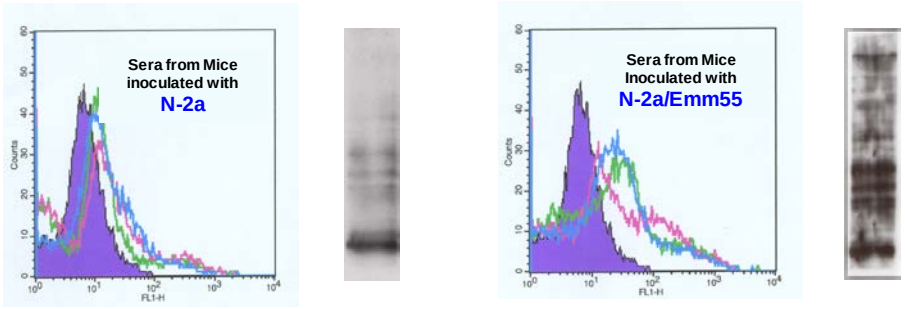
Therapeutic Effect of N-2a/Emm55 in A/J Mice

			Vaccine Dose		
Group	**Neuroblastoma (N-2a)**	**Mice/Group**	**Day 3**	**Day 8**	**Day 13**
1	$1x10^6$	15	-	-	-
2	$1x10^6$	16	$3x10^6$	-	-
3	$1x10^6$	16	$3x10^6$	$3x10^6$	-
4	$1x10^6$	16	$3x10^6$	$3x10^6$	$3x10^6$
5	$1x10^6$	16	$1x10^6$	-	-
6	$1x10^6$	16	$1x10^6$	$1x10^6$	-
7	$1x10^6$	16	$1x10^6$	$1x10^6$	$1x10^6$
8	-	7	$1x10^6$	$1x10^6$	$1x10^6$
9	-	7	$3x10^6$	$3x10^6$	$3x10^6$
	Total # Mice	**125**			

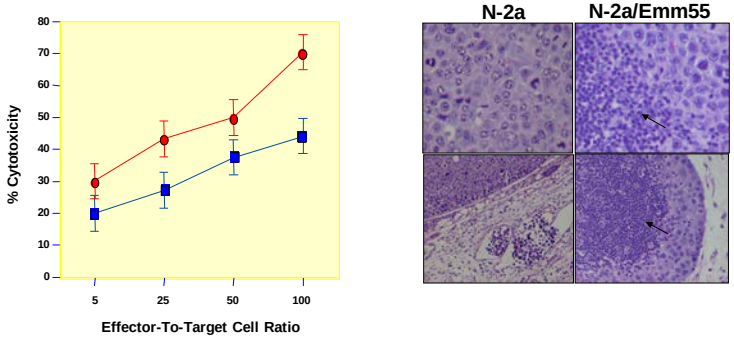
Clinical Response



Humoral Response



Cellular Response



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Summary: Murine Neuroblastoma Studies *N-2a/Emm55*

- Strong humoral and cell-mediated responses
- Prevented tumor formation in 100% of mice
- Increased survival in challenged mice by 81%
- Increased long-term survival by 88%
- Dose-dependent therapeutic effect
- No side-effects observed

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Canine Lymphoma Study

IFx-CL™

- Dogs (n=20) with naturally occurring lymphoma
- Dosed with irradiated autologous lymphoma cells transfected with plasmid DNA (*emm55*)
  - 1 x 10^7 cells / dose
  - 2 - 35 doses / dog; Average = 8 doses
  - Route of administration (IV, SC or ID)
  - Standard protocol: 4 weekly ID injections followed by 4 monthly injections @1 x 10^7 cells / dose

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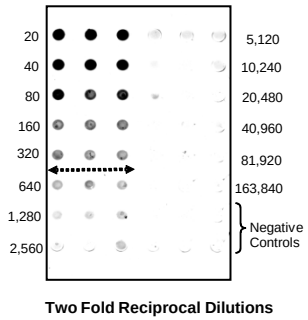
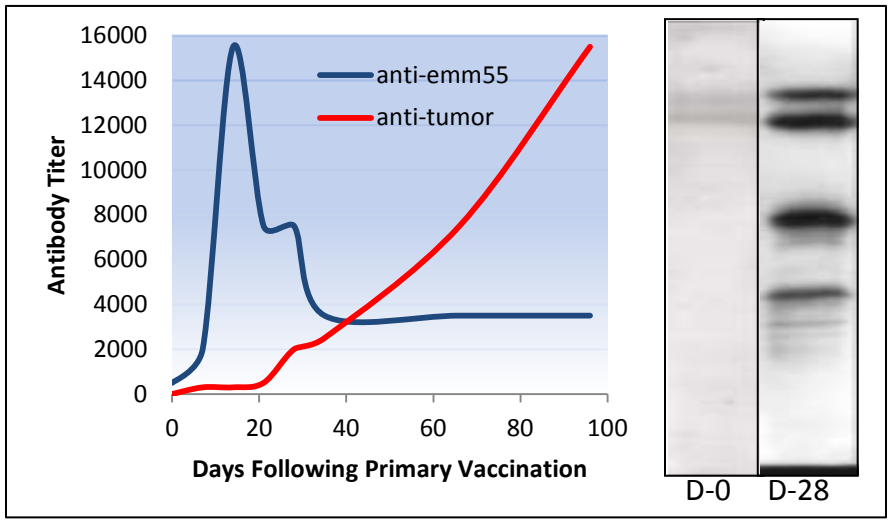
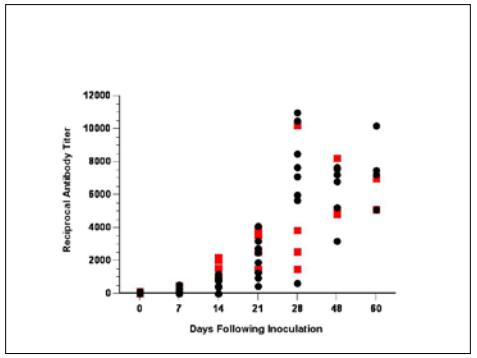
Immune Response to *IFx-CL™*

Humoral

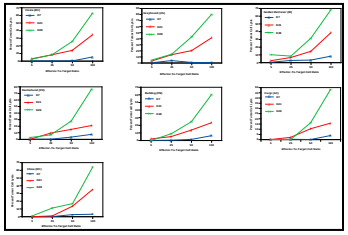


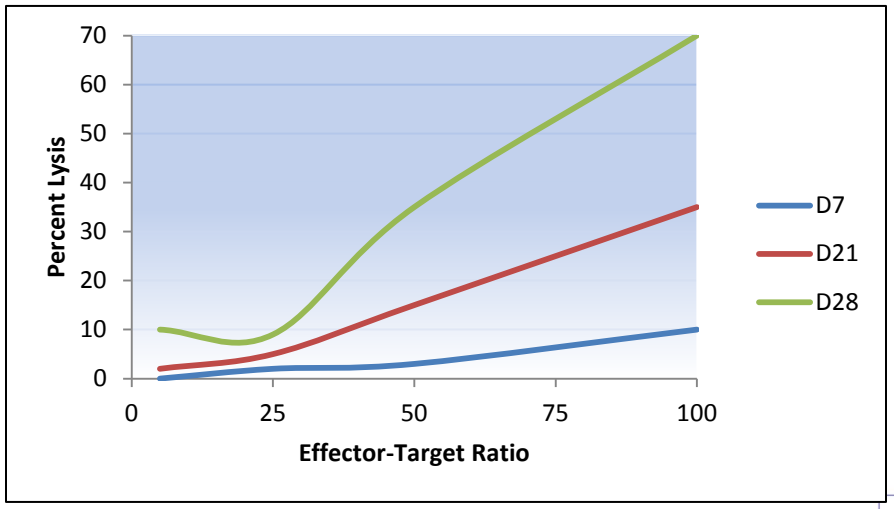
Two Fold Reciprocal Dilutions

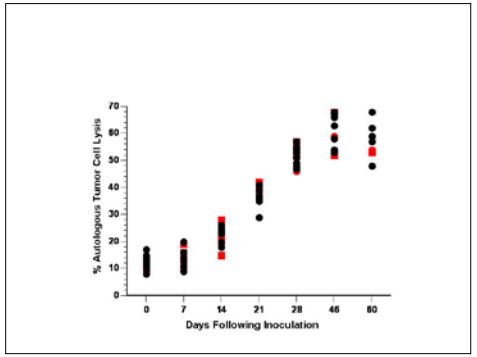




Cellular







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Summary: Canine Lymphoma Study
IFx-CL™

- Strong humoral & cellular-mediated responses
- Enhanced survival
  - Untreated: 14-60 days
  - Vaccine alone: 222 days
  - Vaccine + chemotherapy: 230 days
- No side-effects observed
- Outbred population with spontaneous disease considered best model for human NHL

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Proposed Clinical Study

Phase Ib study using patient-derived tumor cells expressing a streptococcal antigen in asymptomatic patients with indolent non-Hodgkin lymphoma

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Study Objectives

- Primary Objective
  - To assess the safety, tolerability, and feasibility of vaccination with Emm55-expressing autologous tumor cells (IFx-hu1.0) in patients with iNHL
- Secondary Objective
  - To assess the anti-tumor immune responses induced by IFx-hu1.0 in patients treated with the vaccine
  - To note tumor response

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Study Population

- Asymptomatic untreated or previously treated patients with iNHL
  - FDA has recommended that only untreated patients be enrolled in the study
- May include patients with advanced-stage or bulky disease if asymptomatic
- Excludes symptomatic patients and those who have recognized indications for immediate therapy
  - As recommended by the FDA

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Study Design

- Male and female (n=20) patients with iNHL will receive $1x10^7$ cells per dose administered intradermally
- Doses administered weekly for 4 weeks (4 doses) and monthly for 4 months (4 doses) for a total of 8 doses
- Dosing based on murine and canine studies conducted with ImmuneFx™

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Inclusion Criteria

- Histologically confirmed Grade 1 follicular lymphoma, Grade 2 follicular lymphoma, marginal zone lymphoma, mantle cell lymphoma, or lymphoplasmacytic lymphoma that is previously untreated or has relapsed after receiving prior chemotherapy or radiation therapy
- Presence of a lymph node (at least 1.5 cm x 1.5 cm non-necrotic), (either a single lymph node or combined volume of lymphoid tissue) accessible for biopsy/harvest for histological confirmation of diagnosis and for manufacture of the vaccine
- Eastern Cooperative Oncology Group (ECOG) Performance score 0-2
- Life expectancy > 6 months
- Immunologically competent as determined by positive skin test with tetanus toxoid, mumps or Candida
- Adequate blood counts, coagulation parameters, hepatic, renal and clinical chemistries

Exclusion Criteria

- Evidence of transformation to an aggressive form of lymphoma
- Immunocompromised or serious co-morbidities
- Positive anti-double stranded DNA antibodies
- Prior total body irradiation
- Prior splenectomy
- History of allergic reactions attributed to *Streptococcus* species
- Chemotherapy, radiotherapy, biological therapy (antibodies) or endocrine therapies for lymphoma within the last 8 weeks
- Concurrent chronic (more than twice monthly) oral, inhaled or topical corticosteroids use
- Known hepatitis B, hepatitis C, or HIV infection
- Undergoing renal dialysis
- History of organ allograft transplantation
- Participation in a clinical trial within the last 3 months or ever participated in a cancer vaccine trial
- Other malignancy within the past 2 years except non-basal cell skin cancer or carcinoma in situ of the cervix

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Schedule of Study Events

Procedures	Screening Day -7 to 0	Study Week 1	Week 2	Week 3	Week 4	Month 2	Month 3	Month 4	Month 5	Follow-up (Month 7)
Informed consent Eligibility	X									
Physical exam, weight	X									X
Medical history	X									
Concomitant meds.	X									
AEs/SAEs		X	X	X	X	X	X	X	X	X
In-clinic study drug dosing		X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X
Blood for Immune Response Evaluation (blood drawn immediately before vaccine dose given)		X			X			X		X
Clinical labs	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X
Urine pregnancy	X									
ECG	X									X
CT and/or PET scan	X									X

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Stopping rules

- Patient stopping rules
  - Development of intolerable side effects
  - Significantly abnormal lab values
  - Pronounced clinical deterioration or clinical status needing in-patient admission
  - Alternate therapy needed
- Study stopping rules
  - Grade 3-4 toxicity (CTCAE)

Summary
IFx-hu1.0 Whole Cell Vaccine

- Active immunotherapy
- Supported by extensive pre-clinical studies in mouse model and dogs with naturally occurring cancer
- Presents all possible TAA/TSA to the immune system
  - Overcomes tolerance to multiple TAA/TSA
- Targets APC in the dermis for increased specificity
- Initiates and maintains active humoral, cytotoxic T cell and memory immune responses
- Enrollment in this study should not prevent further therapeutic options

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Thank you

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